Remarks and Arguments

Status of the Claims

Claims 15-16, 18, 21-26 and 29 were previously pending and stand rejected.

Amendments to the Claims

Claim 29 is hereby canceled.

No new matter is added as a result of the present amendments to the claims.

Each of the present amendments is made without prejudice. Applicant reserves the right to pursue any subject matter canceled as a result of the present amendments in future prosecution, either in this application or in one or more continuing applications.

Claim Rejections under 35 U.S.C. §102

Claim 29 was rejected under 35 U.S.C. §102 as being anticipated by Grabstein *et al.* (US Patent No. 5,162,111). Without conceding the merits of this rejection, claim 29 is hereby canceled. As such, this rejection moot and Applicant respectfully requests its withdrawal.

Claim Rejections Under 35 U.S.C. §103

Claims 16, 18, and 21-26 were rejected under 35 U.S.C. §103 as being obvious over Grabstein *et al.* (U.S. Patent No. 5,162,111) in view of *Grzybowski et al.* (*Int. J. Pharmaceuticals* 184, pp. 179-187, 1999), further in view of Sampathkumar (U.S. Patent No. 4,804,530). Applicant traverses this rejection.

Combination of the Cited References does not Result in the Claimed Methods

The Grabstein *et al.* reference is cited for teaching that bacterial infections can be treated with systemic application of GM-CSF. The Grzybowski *et al.* reference is cited for the teaching that dressings containing either G-CSF or GM-CSF can be prepared, and that the G-CSF dressings can be applied to a wound to stimulate healing. The Examiner has previously acknowledged that neither Grabstein *et al.* nor Grzybowski *et al.* teach or suggest treating a

localized bacterial infection or bacterial related disease selected from a periodontal disease or sinusitis (see Office Action dated December 23, 2008, page 9). To cure this deficiency, the Examiner relies on Sampathkumar for the teaching that diseases such as periodontal disease can involve bacterial infection.

The deficiency of Grabstein *et al.* and Grzybowski *et al.*, however, is not simply that these references do not disclose treating periodontal disease or sinusitis (although Applicant agrees with the Examiner that they do not). Rather, a primary deficiency of Grabstein *et al.* and Grzybowski *et al.* is that neither teaches or suggests, alone or in combination, treating **localized** bacterial infection by **locally administering** a therapeutically effective amount of a **GM-CSF** polypeptide. Thus, regardless of the nature of the infection, bacterial or otherwise, Grabstein *et al.* and Grzybowski *et al.* do not teach treating it by locally administering GM-CSF. Simply calling out periodontal disease as a bacterial infection, the proposition for which the Examiner cites Sampathkumar, does not address the shortcomings of Grabstein *et al.* and Grzybowski *et al.*, namely the failure to disclose localized treatment of a localized bacterial infection with GM-CSF. Thus, even if the disclosures of Grabstein *et al.*, Grzybowski *et al.*, and Sampathkumar were combined, such a combination would not result in the subject matter of the pending claims.

Moreover, in the Advisory Action dated March 16, 2009 the Examiner argues that Grzybowski *et al.* teach that the art discloses using GM-CSF to treat bacterial infections, and specifically points to an article by Schneider and Dschner (1998) referred to in Grzybowski *et al.* A closer reading of this section of Grzybowski *et al.*, however, reveals that Schneider and Dschner disclose that "G-CSF and, to a lesser extent GM-CSF, may be used as the valuable complementary drugs for **systemic** treatment of bacterial and fungal infections" (emphasis added). Thus, far from disclosing GM-CSF's utility in local administration to treat localized bacterial infections, as presently claimed, Grzybowski *et al.*'s citation to Schneider and Dschner reinforces Applicant's position that none of Grabstein *et al.*, Grzybowski *et al.*, or Sampathkumar, alone or in combination, teach or suggest treating localized bacterial infection by locally administering a therapeutically effective amount of a GM-CSF polypeptide.

GM-CSF vs. G-CSF

Second, in the Advisory Action mailed March 16, 2009, the Examiner asserts that Applicant is arguing features that are not recited in the pending claims. Specifically, the Examiner asserts that "arguments that the antimicrobial effect of G-CSF does not necessarily mean that this cytokine will accelerate wound healing" are not persuasive since wound healing is not recited in the pending claims.

For clarity of the record, Applicant did not, and does not presently, argue that the G-CSF disclosed by Grzybowski *et al.* is ineffective in wound healing. Rather, Applicant asserted that any clinical results achieved by Grzybowski *et al.* with G-CSF are not predictive of results that would be achieved with GM-CSF given the **considerable differences between the two polypeptides**. In fact, Grzybowski *et al.* themselves note these differences. For example, on page 185, Grzybowski *et al.* disclose that "The antimicrobial effect of rhG-CSF does not necessarily mean that this cytokine will accelerate healing of the all types wounds [sic] *in vivo*. In fact, Jyung and co-workers were not able to detect any significant effect of the recombinant rat G-CSF (rrG-CSF) on the healing process of the wounds in rats whereas rrGM-CSF led to the markedly enhances healing…" Thus, even the art cited by the Examiner acknowledges that GM-CSF and G-CSF exhibit different and unpredictable *in vivo* properties. Applicant reiterates that Grzybowski *et al.* only treat bacterial infections *in vivo* using G-CSF, and never reduce to practice *in vivo* treatment with GM-CSF.

Thus, Applicant's point was simply that due to the difference between the two polypeptides, Grzybowski *et al.*'s local administration of **G-CSF** to treat wound healing is not predictive of results that would be achieved with localized treatment of localized bacterial infection with **GM-CSF**, as disclosed by Applicant and recited in the presently pending claims.

The Presently Claimed Methods Achieve Highly Effective Clinical Results

Finally, the present application discloses actual reduction to practice of locally administering GM-CSF to treat periodontal disease and sinusitis, both of which are localized bacterial infections, and that such local administration is highly effective. Indeed, Example 1 shows that local administration of GM-CSF abolished the periodontal disease symptoms, and tooth attachment to the jawbone was regained. Moreover, the patient in Example 1 exhibited freedom from chronic sinusitis for three years after local treatment with GM-CSF. Similarly, the

patient in Example 2 exhibited freedom from periodontal disease symptoms for one year following local treatment with GM-CSF.

Systemic administration and local administration of the same compound can result in dramatically different clinical outcomes, both in terms of effectiveness and adverse effects. For example, Zhang *et al.* (cited on the Information Disclosure Statement filed with this submission) disclose that local administration of insulin to treat wound healing avoids a hypoglycemic effect that is observed with systemic administration (see e.g., page 264, top of 1st column). Indeed, one advantage of local administration is that high levels of a given compound may be achieved in a localized area without subjecting the entire body to such high levels of that compound, which may result in adverse side effects in non-target tissue. Moreover, local administration is useful in situations where it is not possible to administer a compound systematically such that it reaches the target organ (e.g. eye drops).

Conversely, systemic administration may be advantageous in situations where it is difficult or impossible to reach target tissues via local administration. For example, administration of a given compound to an internal organ would be difficult and would require substantial distress to the patient if only local administration were employed. Additionally, systemic administration may be advantageous in situations where the initially high concentration of a given compound resulting from local administration is rapidly decreased. One example of the phenomenon occurs in the case of certain treatments of pneumonia, where administration of antibiotics via inhalation is not fully effective since the antibiotic is transported out of the lungs and into the bloodstream, resulting in an insufficient concentration of the antibiotic in the lungs. In this situation, systemic administration of the antibiotic achieves the concentrations needed to combat the infection in the lungs.

Thus, the fact that a compound may be effective for a given indication when administered systemically, such as the systemic administration of GM-CSF by Grabstein *et al.*, is not predictive of the compound's effect when administered locally for a different indication, such as local administration of GM-CSF to treat a localized bacterial infection, as recited in the pending claims. Aside from failing to teach or suggest the methods recited in the currently pending claims, the cited art does not even contemplate the different results that can be achieved with local administration of GM-CSF to treat a localized bacterial infection.

In contrast, the present application discloses that such local administration is highly effective to treat several localized bacterial infections (see e.g., Examples 1 and 2). Indeed, the present application discloses in paragraph [0033] that "It is a very advantageous feature of the present invention that localized bacterial infections and bacterial related diseases may be treated by local delivery of small doses of the inventive composition in a limited part of the body without any substantial systemic effect on the subject treated."

For at least the reasons presented herein, the rejection of the currently pending claims based on the combination of Grabstein *et al.* and Grzybowski *et al*, and Sampathkumar is improper, and Applicant respectfully request that this rejection be withdrawn.

In light of the present amendments and arguments, Applicant submits that the present application is in condition for allowance, and respectfully requests a notice to that effect. If the Examiner feels that it would further prosecution or expedite allowance of the present case, she is invited to telephone the undersigned at 612-766-2071

Please charge any fees, or apply any credits or previous overpayments, to deposit account 06-1050, referencing Attorney Docket No. 15665-0010US1.

Respectfully submitted,

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